

## **PTAC meeting held 16 & 17 February 2012**

### **(minutes for web publishing)**

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note:

- that this document is not necessarily a complete record of the PTAC meeting; only the relevant portions of the minutes relating to PTAC discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) in order to:

- (i) enable PHARMAC to carry out, without prejudice or disadvantage, commercial activities (section 9(2)(i)); and/or
- (ii) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j));

## Contents

1	Record of PTAC meeting held November 2011 .....	3
2	Subcommittee minutes .....	3
3	Dutasteride for Benign Prostatic Hyperplasia.....	3
4	Certolizumab for Rheumatoid Arthritis .....	5
5	Vemurafenib for melanoma – BRAF V600 mutation .....	7
6	Methotrexate Prefilled Syringes .....	9
7	Indacaterol for chronic obstructive pulmonary disease.....	11
8	MS Treatments.....	13
9	Fingolimod for multiple sclerosis.....	14
10	Lead Poisoning.....	17
11	Genetic and platelet function testing in targeting antiplatelet therapy.....	19
12	Eculizumab for paroxysmal nocturnal haemaglobinuria .....	21
13	Eltrombopag for idiopathic thrombocytopenic purpura .....	23

## 1 Record of PTAC meeting held November 2011

1.1 The Committee reviewed the minutes of the PTAC meeting held on 10 & 11 November 2011, and made the following amendments:

1.1.1 Paragraph 13.9.4 (8.9.4 in web version) change: “mean duration being 277 days (interquartile range of 179 to 365 days)” to “median duration being 276 days”.

## 2 Subcommittee minutes

2.1 Cardiovascular Subcommittee – 23 September 2011

2.1.1 The Committee noted and accepted the record of the meeting in relation to items, Conflicts of Interest, Minutes of the Previous Meeting and Dronedarone for Atrial Fibrillation.

2.1.2 The Committee noted that the remainder of the record related to hospital pharmaceuticals that PTAC would be formally reviewing at its May 2012 meeting.

2.1.3 The Committee noted the Subcommittee’s recommendation that prasugrel be funded with a high priority for patients undergoing percutaneous coronary intervention (PCI) who are clopidogrel-allergic and patients who experience stent thrombosis whilst on clopidogrel. The Committee noted that it had previously recommended that prasugrel be funded with low priority for these two patients groups and PHARMAC will be consulting on funding the clopidogrel-allergic group shortly but the application for the stent thrombosis was not being progressed at this stage due to low cost-effectiveness relative to PHARMAC’s other funding priorities. The Committee considered that evidence is lacking for prasugrel in patients who have experienced stent thrombosis whilst on clopidogrel, but it is unlikely that any evidence will become available for this patient group. Therefore, the Committee amended its funding recommendation for this patient group from low priority to medium priority.

## 3 Dutasteride for Benign Prostatic Hyperplasia

### Application

3.1 The Committee considered an application from GlaxoSmithKline for the listing of dutasteride (Avodart) on the Pharmaceutical Schedule for the treatment of patients with benign prostatic hyperplasia under the same special authority as finasteride.

### Recommendation

3.2 The Committee **recommended** that dutasteride be listed on the Pharmaceutical Schedule subject to the following Special authority criteria only if cost neutral :

Initial application from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Both:

1 Patient has symptomatic benign prostatic hyperplasia; and

2 Either:

2.1 The patient is intolerant of non-selective alpha blockers or those are contraindicated: or

2.2 Symptoms are not adequately controlled with non-selective alpha blockers.

Note Patients with enlarged prostates are the appropriate candidates for therapy with dutasteride.

The decision criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (ii) *The particular health needs of Maori and Pacific peoples;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

## Discussion

- 3.3 The Committee noted that dutasteride is a potent, selective and irreversible type 1 and type 2 5-alpha-reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterone intracellularly, slowing prostate growth and alleviating BPH symptoms. The Committee noted that dutasteride has similar indications to finasteride, which is a type 2 5-alpha-reductase inhibitor, although Medsafe is currently considering an extension of dutasteride's registered indication to allow concomitant use with an alpha blocker.
- 3.4 The Committee reviewed the only randomised controlled trial for the proposed indication. ARI40001 was a Phase IIIb multinational, multicentre, double-blind, double-dummy, randomised, 12 month study published by Nickel et al BJU International 2011;108(3):388-394 and compared dutasteride and finasteride in the treatment of benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). The study consisted of a 4 week placebo run-in period followed by 12 month double-blind phase where patients received either dutasteride 0.5 mg od or finasteride 5 mg od followed by an optional 24 month open label extension with a three monthly follow up.
- 3.5 The Committee noted that 1630 men were randomised with the primary endpoint being the change in prostate volume and secondary endpoints of an improvement in American Urological Association Symptom Index (AUA-SI) scores, improvement in  $Q_{max}$  and long term safety in the open label phase.
- 3.6 The Committee noted that at month 12 the reduction in prostate volume was 26.7% in the dutasteride group and 26.3% in the finasteride group. Similar reductions in AUA-SI and  $Q_{max}$  were observed in both groups although in AUA-SI sub-group analysis of subjects with a history of alpha blocker use compared to no prior history of alpha blocker use a statistically significant difference was noted at month 12 for dutasteride.
- 3.7 The Committee noted that sexual adverse events (impotence, decreased libido and ejaculation disorders) were the most common with similar incidence in both groups. The incidence of new sexual adverse events decreased over time and the incidence of head aches increased. Prostate cancer was reported in four men from the finasteride group and three from the dutasteride group.
- 3.8 In summary, the Committee noted that over a 12 month period finasteride and dutasteride exhibit similar efficacy and safety. The Committee noted that the strength and quality of the evidence was moderate but that a weakness of the study is that prostate volume may not fully correlate with clinical efficacy and may not be the most suitable surrogate endpoint for AUR and BPH-related surgery.

- 3.9 The Committee reviewed the second study (AR140005), a four year, multicentre, randomised, double-blind, parallel-group study published by Roehrborn et al Eur Urol 2010;57: (123-131) comparing the effects of combination therapy of dutasteride with tamsulosin versus dutasteride or tamsulosin monotherapy. Patients were randomised to one of the following once daily treatments for four years: dutasteride 0.5 mg and tamsulosin 0.4 m, dutasteride 0.5 mg with tamsulosin-matched placebo or dutasteride-matched placebo and tamsulosin 0.4 mg.
- 3.10 The Committee noted that 4844 men were randomised with the primary endpoint at year four being the time to the first event of AUR or BPH-related surgery and secondary endpoints BPH clinical progression, symptoms,  $Q_{max}$ , prostate volume, safety and tolerability. There was no significant difference in time to the first AUR or BPH related surgery between dutasteride monotherapy and combination or in maximum urinary flow rate and prostate volume at 4 years. The Committee noted that there were significant differences favouring combination therapy in BPH Clinical progression and IPPS score at 4 years.
- 3.11 The Committee noted that overall dutasteride appears well tolerated with no significant adverse events. In addition to the trials, GSK provided the 14<sup>th</sup> Periodic Safety Update Report (PSUR) which represents an estimated post marketing exposure to dutasteride of 852,000 patient years and the summary is that the benefit/risk profile of dutasteride monotherapy for the treatment of BPH continues to be favourable. The Committee noted that ongoing pharmacovigilance is aimed at continuing to monitor hepatobiliary disorders, male breast cancer, prostate cancer and cardiac failure. To date these potential adverse events occur rarely with an incidence of <1%.
- 3.12 The Committee noted that epidemiology studies suggest that Pacific peoples have greater symptom severity and reduced QOL compared to both Maori and European. Pacific Islanders and Maori are less likely to visit a doctor compared to Europeans, although the prevalence of BPH is the same across all ethnicities. The Committee considered that if listed, dutasteride would take a share of the finasteride market and noted that dutasteride may have theoretical advantages over finasteride but these have not been demonstrated in comparative clinical trials.

## 4 Certolizumab for Rheumatoid Arthritis

### Application

- 4.1 The Committee considered an application from UCB Pharma for the funding of certolizumab pegol (Cimzia) for patients with moderate to severe active RA in adult patients.

### Recommendation

- 4.2 The Committee **recommended** that, since there is only short term evidence for certolizumab pegol, and little clinical need and limited benefit to be gained from funding a third TNF inhibitor, that the application be declined.
- 4.3 The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (ii) *The particular health needs of Maori and Pacific peoples;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding*

*pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## **Discussion**

- 4.4 The Committee noted that certolizumab pegol is a novel TNF inhibitor consisting of a humanised FAB fragment fused to a polyethylene glycol moiety. Members noted that the half life of certolizumab pegol is approximately 14 days which is similar to the currently funded monoclonal antibody adalimumab. Members noted that certolizumab pegol comes in a prefilled syringe and is administered subcutaneously at a dose of 400 mg every two weeks for 3 doses, then 200 mg every two weeks thereafter.
- 4.5 The Committee noted that the applicant had requested certolizumab pegol be listed subject to Special Authority similar to that of adalimumab and etanercept and that certolizumab pegol be recommended as the first TNF inhibitor, i.e. used prior to adalimumab and/or etanercept.
- 4.6 The Committee considered that the key published evidence in support of the application comprised two randomised, placebo controlled phase III studies of certolizumab pegol in combination with methotrexate in patients with active rheumatoid arthritis who have an incomplete response to methotrexate (RAPID-1 Keystone et al 2008 and RAPID-2 Smolen et al, 2009) and one randomised, placebo controlled phase III study of certolizumab pegol monotherapy in patients who have previously failed at least one DMARD (FAST4WARD - Fleischmann et al, 2009).
- 4.7 The Committee also noted evidence from a fourth, unpublished, study (CDP870-014) which examined an alternative dosing schedule of certolizumab (400 mg subcutaneously every 4 weeks) in combination with methotrexate compared to methotrexate alone in patients with RA who are partial responders to methotrexate.
- 4.8 The Committee noted that RAPID-1 and RAPID-2 were similar in design and patient population enrolled, patients were randomised 2:2:1 to certolizumab pegol 400mg weeks 0, 2, 4 followed by 200mg or 400mg every two weeks thereafter, or placebo. Members noted that less than 5% of the patients enrolled had received prior biologic therapy. Members noted that RAPID-1 used a lyophilised formulation of certolizumab pegol and RAPID-2 used a liquid formulation, both formulations were considered bioequivalent.
- 4.9 The Committee noted at 24 weeks ACR 20, the primary endpoint in both studies, was significantly improved in certolizumab pegol treated patients; 59% and 57% for RAPID 1 and 2 respectively, compared with 14% and 9% for placebo. Members noted that in FAST4WARD, certolizumab pegol monotherapy also improved ACR20 compared with placebo (46% vs 9%), however, the responses were not as high as in the two RAPID studies where certolizumab pegol was administered in combination with methotrexate.
- 4.10 The Committee noted that there were no studies directly comparing certolizumab pegol with other TNF inhibitors. Members considered that adalimumab was the primary comparator due to its similar dose frequency and mode of action. Members noted the applicant presented extensive indirect analyses comparing ACR20, 50 and 70 responses of certolizumab pegol with adalimumab at various time points (12, 14/16 and 24 weeks). Members considered that evidence demonstrated that certolizumab pegol was similar to adalimumab in terms of efficacy.

- 4.11 The Committee considered that the side effect profile of certolizumab pegol was also similar to that of other TNF inhibitors, comprising infection, injection site reaction, reactivation or new tuberculous infection and increased risk of malignancy. However, members noted that any consideration of the safety profile of certolizumab was hampered by the short duration of the studies relative to the likely treatment duration in the patient population proposed for funding.
- 4.12 The Committee noted that at the proposed pricing certolizumab would be cost saving compared with adalimumab at least in the short term, however, members considered that if it was funded some patients would be treated with 3 lines of TNF therapy which would increase costs. Members also considered that there was a risk that patients would be treated with higher doses of certolizumab in practice (400 mg every two weeks) and noted that PHARMAC had already received requests for higher doses of adalimumab to be funded.
- 4.13 The Committee noted that efficacy rates drop with subsequent lines of RA therapy which significantly reduces the cost effectiveness for each additional treatment used. Members considered that patients who had already failed two TNF inhibitors should switch to treatment with an alternative mode of action e.g. rituximab, rather than try a third TNF inhibitor. Members considered that there was little clinical need and limited benefits to be gained from funding a third TNF inhibitor and there was significant risk that the funding of certolizumab would grow the market.

## 5 Vemurafenib for melanoma – BRAF V600 mutation

### Application

- 5.1 The Committee considered an application from Roche Products NZ Ltd for the funding of vemurafenib (Zelboraf) for patients with unresectable stage IIIC or stage IV melanoma positive for BRAF V600 mutation.

### Recommendation

- 5.2 The Committee **recommended** that the application be declined.
- 5.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 5.4 The Committee considered that malignant melanoma was a significant health concern in New Zealand. Members noted that New Zealand has a very high incidence of melanoma and it is the fourth most common cancer in NZ. Members noted that risk factors for melanoma are both environmental and genetic. Members considered that effective prevention is the key to minimizing morbidity and mortality in patients with melanoma
- 5.5 The Committee noted that melanoma has a variable disease course with some patients presenting with indolent disease evolving over a period of years whereas others present with very aggressive disease and survive only a few weeks.

- 5.6 The Committee noted that because most patients have poor responses to the main currently funded treatment option, dacarbazine (DTIC), some centres did not routinely provide patients with treatment. Members considered that although DTIC was ineffective for most patients it was well tolerated, and in 5-15% of patients it does produce an objective response. Overall, members considered that there was a high unmet medical need for new effective treatments for patients with malignant melanoma.
- 5.7 The Committee noted that vemurafenib is a new, first in class, orally administered inhibitor of oncogenic BRAF, (v-raf murine sarcoma viral oncogene homolog B1). Members noted that vemurafenib suppresses downstream signalling of BRAF disrupting cell proliferation and survival. Members noted that activating mutations in BRAF are present in approximately 50% of patients with advanced melanoma.
- 5.8 The Committee considered key evidence from one open label phase 3 randomised clinical trial in patients with previously untreated, metastatic melanoma (Stage IIIC or IV) with the BRAF mutations detected using a Roche kit (BRIM-3 Chapman PB et al. N Engl J Med 2011; 364: 2507–16). Members noted that 675 patients were randomly assigned (1:1) to receive either vemurafenib (960 mg orally, 4 tablets, twice daily) or DTIC (1000 mg/m<sup>2</sup> intravenously every 3 weeks).
- 5.9 The Committee noted that the original primary endpoint of the study was overall survival (OS), however, the statistical plan was revised partway through the study such that OS and progression free survival (PFS) became co-primary endpoints. Members also noted that following an interim analysis patients randomised to the DTIC control arm were permitted to switch to vemurafenib.
- 5.10 The Committee noted that the interim analysis median PFS was 5.3 months for vemurafenib treated patients compared with 1.6 months for DTIC (absolute difference of 3.7 months, Hazard Ratio, 0.26; 95% CI, 0.20 to 0.33 p<0.001). Members noted that median OS had not been reached by the interim analysis but that at 6 months, overall survival was 84% (95% CI, 78 to 89) in the vemurafenib group compared with 64% (95% CI, 56 to 73) in the DTIC group. Members considered that median follow-up for the interim analysis was short; 3.8 months for the vemurafenib group and 2.3 months the DTIC group.
- 5.11 The Committee noted that the supplier also provided further, unpublished, follow-up from the BRIM-3 study. Members noted that at the most recent data cut provided (October 2011) median overall survival was 13.21 months for the vemurafenib group compared with 9.92 months for the DTIC group (p=<0.001). Members considered that this result is confounded by the permitted cross-over, with the likely direction of bias working against vemurafenib.
- 5.12 The Committee noted that approximately 1 in 5 of patients treated with vemurafenib developed cutaneous squamous lesions all of which were treated with minor excisional surgery. Members noted that vemurafenib treated patients also experienced more arthralgia and rash compared with dacarbazine. Members noted that there were no formal quality of life data presented.
- 5.13 The Committee considered that vemurafenib provided a small, 3.7 month, benefit in PFS over DTIC treatment. Members noted that this benefit did not appear to be maintained beyond 8 months.
- 5.14 The Committee noted that the suppliers own cost effectiveness analysis indicated that vemurafenib had a very high cost per QALY compared with other treatments. Members considered that in its cost effectiveness modelling the supplier had overestimated the long

term benefits for vemurafenib and considered that a proportional hazards model was not appropriate given the available evidence.

- 5.15 The Committee considered that overall vemurafenib was a very high cost treatment that provided only a small, short term, benefit.

## 6 Methotrexate Prefilled Syringes

### Application

- 6.1 The Committee considered an application from PHARMAC staff for the listing of methotrexate pre-filled syringes on the Pharmaceutical Schedule.

### Recommendation

- 6.2 The Committee **recommended** that methotrexate prefilled syringes should be funded on the Pharmaceutical Schedule subject to Special Authority criteria for patients with Rheumatoid Arthritis, Juvenile Idiopathic Arthritis or Psoriasis unable to take methotrexate tablets. The Committee gave this recommendation a low priority.
- 6.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

### Discussion

- 6.4 The Committee noted that methotrexate is the primary disease-modifying antirheumatic drug (DMARD) used in inflammatory conditions and it is also commonly used in oncology patients albeit generally at higher doses.
- 6.5 The Committee noted that PHARMAC staff had received a number of requests from pharmacists and other parties to fund prefilled syringe presentations of methotrexate in the community for patients with autoimmune conditions, mainly Rheumatoid Arthritis (RA) requiring methotrexate injections. Members noted that because methotrexate is a cytotoxic agent the requesters considered there were safety risks for health care providers and patients from the handling, administering and disposal of the currently funded vial presentation of methotrexate in the community.
- 6.6 The Committee noted that until recently no registered pre-filled syringe presentation of methotrexate was available, however, PHARMAC recently ran a tender for methotrexate pre-filled syringes and products were now available. Members considered that in the community parenteral methotrexate is primarily used in inflammatory conditions such as RA, Juvenile Idiopathic Arthritis (JIA), Psoriasis and perhaps Crohn's Disease. Members noted that the maximum recommended dose of methotrexate is 25mg/week in RA, 30 mg/week in Psoriasis and 10-15 mg/m<sup>2</sup> in JIA patients. Members considered that there was good evidence to support the efficacy of parenteral methotrexate in patients with these conditions.

- 6.7 The Committee considered that parenteral methotrexate is primarily used in patients who have inadequate response to, or who are unable to orally take, methotrexate tablets. Members considered that the majority of patients requiring parenteral methotrexate in the community are currently being dispensed funded vials and syringes and either self-administering methotrexate subcutaneously, or district nurses may be visiting the patient to administer the injections. Members also noted that some DHBs hospital pharmacies are dispensing methotrexate pre-filled syringes to patients in the community, with the pre-filled syringes being sourced from a third party compounder, or compounded in-house.
- 6.8 The Committee considered that because most patients are dispensed 50 mg vials, whereas, dosing is generally between 25-30 mg weekly, dispensing the currently funded vials may lead to cytotoxic waste in the community and potential for overdose or incorrect dosing. Members also considered that funding pre-filled syringes may reduce the risk of spillage and contamination compared with vials.
- 6.9 The Committee noted that whilst there was good evidence to support the efficacy of parenteral methotrexate in patients with various inflammatory conditions compared with oral presentations, there was no data comparing the efficacy and safety of pre-filled syringes compared with vials. Therefore, members considered it difficult to determine the magnitude of any health gain that would be obtained from funding of pre-filled syringes.
- 6.10 The Committee noted a recent Australian study (Wong et al Internal Medicine Journal 2009) examining serum and urine concentration of methotrexate in volunteers following deliberate skin exposure to 25 mg methotrexate solution that concluded that complex oncology cytotoxic handling protocols used for methotrexate are unnecessary for rheumatology patients and their carers because of the much lower doses used. The study showed that deliberate skin exposure for 30 minutes, and possible inhalation, of methotrexate solution failed to result in any significant or quantifiable systemic absorption or toxicity.
- 6.11 The Committee noted a report from China (Deng HP et al, Mutagenesis 2005) that compared 21 factory workers occupationally exposed to methotrexate, with 21 controls matched for age, gender and smoking. This found evidence of genetic damage in a set of 4 standard assays. While the Committee considered it unlikely that health care professionals and patients would reach the same cumulative exposure as these Chinese factory workers, the Committee considered this to be relevant evidence for the potential risk of sustained environmental exposure to methotrexate.
- 6.12 The Committee considered that although methotrexate is a cytotoxic agent the doses used in inflammatory conditions are generally much lower than those used in oncology and the risk of adverse effects to health care professionals and patients from handling methotrexate was very low. However, members considered that there was a perception of risk amongst health care professionals which may lead to inequitable access to parenteral methotrexate for patients.
- 6.13 The Committee noted that the cost of methotrexate pre-filled syringes was significantly higher than currently funded vial presentations [ withheld under s 9(2)(i) and 9(2)(j) of the OIA ]. Members considered that because of their increased convenience, and ease of handling, pre-filled syringes would replace vials in the community and the market for parenteral methotrexate could grow significantly. Members considered that some of the additional cost may be offset by a reduction in district nurse/pharmacist resources for managing and administering the currently funded vial presentations. Members also considered having access to a more convenient presentation of parenteral methotrexate

may delay initiation of more expensive biologic therapies (e.g. adalimumab and etanercept) in a small number of patients.

- 6.14 The Committee considered that overall there was no evidence to suggest the funding methotrexate pre-filled syringes would improve safety or provide better health outcomes for patients or caregivers compared with currently funded vials. However, members supported the funding of pre-filled syringe presentations for patients as it would provide a more convenient presentation for use in a community setting. Members did not consider it appropriate, or necessary, to fund pre-filled syringes for oncology patients.

## 7 Indacaterol for chronic obstructive pulmonary disease

### Application

- 7.1 The Committee considered an application from Novartis for listing of indacaterol (Onbrez Breezhaler) on the Pharmaceutical Schedule for the treatment of patients with chronic obstructive pulmonary disease (COPD). Novartis proposed indacaterol be listed under a new therapeutic group “Inhaled Ultra-Long acting Beta-adrenoceptor Agonist” with a Special Authority.

### Recommendation

- 7.2 The Committee **recommended** that indacaterol be listed on the Pharmaceutical Schedule only at a price that is cost neutral to a Long-acting Beta-adrenoceptor Agonist (LABA).
- 7.3 The decision criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 7.4 The Committee noted that indacaterol is a once daily  $\beta_2$ -adrenergic agonist with an adrenergic receptor selectivity profile similar to eformoterol.
- 7.5 The Committee noted that the evidence of efficacy submitted by Novartis came from a series of randomised controlled trial funded by Novartis. The trial were conducted on similar populations with similar inclusion criteria: participants  $\geq 40$  years, 10 to 20 or more pack years of smoking history and moderate/severe GOLD defined COPD ( $FEV_1 < 80\%$  and  $\geq 30\%$  predicted and  $FEV_1/FEV < 70\%$ )<sup>1</sup>. Exclusions included history of asthma and, in a number of trials, a recent change in medication, respiratory infection or exacerbation. The Committee noted that the mean age of participants in the trials was mid sixties with the proportion of severe COPD participants being less than 50%. The Committee noted that this creates extrapolation issues when comparing to the New Zealand population who are treated with tiotropium as they are likely to be older with more severe disease.

---

<sup>1</sup> At its May 2012 meeting the Pharmacology and Therapeutics Advisory Committee reviewed these minutes and made the following amendment. Paragraph 7.5 change: “ $FEV_1/FEV < 70\%$ ” to “ $FEV_1/FVC < 70\%$ ”.

7.6 The Committee noted that all of the trials used FEV<sub>1</sub> at 12 weeks as a primary outcome measure of efficacy, which is a well established endpoint in COPD trials with good correlation to clinical severity, although uncertainty remains around the correlation of small improvement in FEV<sub>1</sub> to more clinically relevant endpoints. The Committee noted that the trials were often not appropriately powered for endpoints of the clinically important outcomes of interest for long term treatment of COPD medication such as Quality of Life measures (e.g. the St. Georges Respiratory Questionnaire (SGRQ)), exacerbations, hospitalisation and mortality.

7.7 The Committee reviewed several trials supplied by the sponsor.

- INHANCE (Donahue et al, Am J Resp Crit Care Med 2010;182:155-62) a double blind randomised controlled trial of indacaterol vs. formoterol 12µg BD vs. placebo vs. open label tiotropium 18µg od of 26 weeks duration. The study design first utilised an adaptive seamless design to compare four doses of indacaterol (75 µg vs. 150 µg vs. 300 µg vs. 600 µg) at two weeks in order select two doses for further study. Indacaterol 150 µg and 300 µg were selected on efficacy and safety endpoints for further study versus tiotropium 18 µg and placebo in the second arm of the study. Improvement in FEV<sub>1</sub> and SGRQ between both indacaterol groups and the placebo group were found at weeks 12 and 26. There was no clinical difference between the indacaterol groups and tiotropium in FEV<sub>1</sub>, SGRQ or exacerbations.
- INDORSE (Chapman et al, Chest 2011;140:68-75) a 26 week planned extension of the indacaterol and placebo arms of the INHANCE study, double blind versus placebo. FEV<sub>1</sub> differences persisted at 52 weeks, fewer exacerbations occurred in the indacaterol groups vs. placebo (0.39 and 0.38/year versus 0.54/year). Worsening COPD (24-27%) and nasopharyngitis (15-18%) were the most common adverse events and were comparable across the two indacaterol groups.
- INLIGHT1 (Feldman et al, BMC Pulmonary Medicine 2010,10:11-18) 416 participants in a 12 week study of indacaterol 150 µg vs. placebo. FEV<sub>1</sub> improved (p<0.001) in the indacaterol group. Other secondary endpoints were also improved, although exacerbations, hospitalisations and HRQoL were not reported.
- INVOLVE (Dahl et al Thorax 2010;65:473-9) 1,732 participants, 52 week double blind, double dummy randomised controlled trial comparing indacaterol 150 µg o.d. and 300 µg o.d. vs. formoterol 12 µg b.d. vs. placebo. FEV<sub>1</sub> improved in the indacaterol groups versus formoterol and placebo (p<0.001). There was no difference between the active treatments in SGRQ scores at 52 weeks and exacerbation rates were similar in all arms.
- INTENSITY (Buhl et al Eur Respir J 2011;as doi:10.1183/09031936.00191810) 1,598 participants in a 12 week double blind, double dummy, randomised controlled trial of indacaterol 150 µg o.d. vs. tiotropium 18 µg o.d. The two treatments had similar overall effects on trough FEV<sub>1</sub>.
- INSIST (Korn et al Resp Med 2011;105:719-726), 1,123 patients in a 12 week double blind, double dummy, randomised controlled trial of indacaterol 150 µg o.d vs. salmeterol 50 µg bd. Primary endpoint was the area under the curve FEV<sub>1</sub> at 12 weeks and was statistically in favour of indacaterol as was the 24hr trough FEV<sub>1</sub>. Adverse events were similar between the two groups.

- INLIGHT2 (Kornman et al Eur Respir J 2011;37:273-279) 1,002 patients in a 26 week double blind randomised controlled trial of indacaterol 150 µg o.d. vs. salmeterol 50 µg b.d. vs. placebo. At 26 weeks FEV<sub>1</sub> in the indacaterol group was 180 ml higher than placebo and 110 ml higher in the salmeterol arm compared to indacaterol and placebo (P<0.001 in both cases). Similar improvements in SGRQ scores of >4 points in both active arms and indacaterol patients required less salbutamol prn and were better able to perform usual duties.

7.8 The Committee considered three other studies:

- INTRUST 1 and 2 (Maher et al unpublished, abstract for poster session at Am Thoracic Society Conference, Denver 2011). 2,271 patients in two twelve week open label double blind randomised indacaterol 150 µg plus open label tiotropium 18 µg vs. open label tiotropium 18 µg plus placebo to indacaterol 150 µg o.d. Both studies showed a 70-80 ml improvement in FEV<sub>1</sub> in the tiotropium plus indacaterol arm vs. tiotropium alone. QoL, exacerbations and hospitalisations were not reported; adverse events were similar.
- Cardio and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. Worth et al Resp Med 2011 105:571-579. report on 4,635 patients from the Involve, Inhance and Insight2 trials. 4.7% receiving indacaterol experienced a cardio/cerebrovascular event of which 46% were arrhythmias giving a relative risk of 1.35(0.94 – 1.92) when compared to placebo – similar to the risks associated with formoterol, salmeterol and tiotropium (although tiotropium relative risk compared to placebo is 1.67 (1.02 – 2.73). Prevalence of serious cardiac/cerebrovascular adverse events was ~2%.

7.9 The Committee considered the quality of the evidence was good for the modest short-term and medium term efficacy when compared to placebo in patients with moderate to severe GOLD defined disease but noted that there is no long term evidence of efficacy in disease progression, and no evidence in mild or in very severe disease.

7.10 The Committee considered that indacaterol has the same or similar biological and therapeutic effect as a LABA and the comparator should be a LABA not tiotropium. The Committee did not consider once-per-day administration over twice-per-day to be sufficient to create a new category of Beta Agonists. The Committee considered that there was no justification to define a new heading in the Pharmaceutical Schedule and that indacaterol should, if funded, be listed as a long-acting beta-adrenoceptor agonist.

## 8 MS Treatments

### Application

8.1 The Committee considered the updated cost utility analysis review by PHARMAC staff, following the submission of a funding application by the Multiple Sclerosis Society of New Zealand and MSTAC proposing to amend the entry criteria to commence treatment with an EDSS of less than 2.0.

### Recommendation

8.2 The Committee **recommended** that access to multiple sclerosis (MS) treatments be amended to commence treatment for patients with established relapsing-remitting MS with an EDSS of less than 2.0 with a low priority.

- 8.3 The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## Discussion

- 8.4 The Committee noted that extending access to patients with established relapsing-remitting MS (RR-MS) to include those with an EDSS of less than 2.0 whilst meeting other access criteria would allow funded treatment for patients with no persistent disability but who have MRI findings diagnostic of MS with or without clinical signs in one or more functional system. The Committee considered that the use of MRI with gadolinium contrast in order to diagnose MS means that clinical signs or attacks of disease were not necessarily essential to the diagnosis of established MS, but that the relationship between disease burden measured by MRI and the clinical effects of disease may be imprecise. The Committee noted that these factors would need to be considered if the entry criteria for funded MS treatments were amended.
- 8.5 The Committee noted that the updated cost-utility analysis by PHARMAC staff indicated improved cost-effectiveness if treatment did not commence until patients have at least some disability associated with MS.
- 8.6 The Committee noted from the updated cost utility analysis results that if treatments were less effective than in the relevant randomised controlled trials (RCTs) in delaying disease progression (i.e. the relative risk of disease progression during treatment were to increase to become closer to 1.0) then treatment would be less cost effective. The Committee further noted the findings of the risk-sharing arrangement in the UK (Boggild et al. BMJ 2009;339:b4677) previously considered by the Committee (February 2010, May 2011), which suggested that in a large cohort study that treatment may be less effective than found in the RCTs.
- 8.7 The Committee noted that treatments are costly and therefore price reductions have an inordinate impact on the cost utility estimates. The Committee noted that there is relatively little sensitivity to utilities associated with EDSS states and to costs associated with EDSS states.
- 8.8 The Committee considered that amending the criteria to fund treatment for patients with an EDSS of 0 but exiting with a two-point deterioration may be difficult to implement given the complexity of the current criteria. Therefore, the Committee considered that if the EDSS entry criteria were reduced to 0, then deterioration to EDSS of 4.0 may need to be considered.
- 8.9 The Committee considered that the cost utility estimates for amending stopping criteria to EDSS 6.0 for all patients may not differ significantly from the current treatment criteria. The Committee further noted that if treatment costs reduced sufficiently, then an amendment to the stopping criteria could be considered.

## 9 Fingolimod for multiple sclerosis

### Application

- 9.1 The Committee considered a funding application from Novartis for fingolimod (Gilenya) for the treatment of relapse<sup>2</sup> remitting multiple sclerosis. The supplier proposed that fingolimod is listed in Section B of the Pharmaceutical Schedule with the same access criteria as applies to other currently funded multiple sclerosis (MS) treatments.

### **Recommendation**

- 9.2 The Committee **deferred recommending** fingolimod for funding until it received further advice from the Neurology Subcommittee and MSTAC and further analysis by PHARMAC staff as to its cost-effectiveness in the context of a number of possible treatment algorithm models.

### **Discussion**

- 9.3 The Committee noted that fingolimod is a sphingosine-1-phosphatase receptor modulator which prevents lymphocytes from crossing the blood brain barrier and causing damage to nerve cells in the brain and spinal cord. The Committee noted the treatment to be a new type of disease modifying treatment (DMT) for MS and that it has similar effects to beta interferon and glatiramer. The Committee considered that fingolimod should be used as monotherapy.
- 9.4 The Committee noted that the goal of MS treatment is to prevent or slow the onset of disability and therefore to maintain the quality of life. The Committee noted that it has not been convinced that the currently funded DMT achieve these outcomes.
- 9.5 The Committee considered that the quality of the pivotal trials were good and the strength moderate, but were not powered to detect reductions in disability progression. The Committee noted that the studies were relatively short for a long term condition with limited data on the dose that is recommended. The Committee considered that there were insufficient long-term data to allay safety concerns raised in the pivotal trials. The Committee considered that the supplier's comparisons with placebo and beta-interferon were appropriate.
- 9.6 The Committee considered a randomised, double-blind, parallel-group, multicentre study (FREEDOMS) evaluating effects of daily fingolimod oral therapy compared with placebo in 1272 patients with relapse remitting MS reported by Kappos et al. (N Eng J Med 2010; 362: 387-401). Patients were randomly assigned (1:1:1) to receive fingolimod 1.25 mg or 0.5 mg capsules or placebo once daily for 24 months. The Committee noted that at baseline, participants were slightly less disabled than patients meeting the NZ criteria, having mean EDSS score at baseline of 2.4 and the annualised relapse rate (ARR) of two relapses in two years or one relapse over the previous year. The Committee also noted that the 0.5 mg fingolimod arm reported significantly reduced rates of relapses and disability progression compared with placebo (ARR 0.18 fingolimod vs 0.40 placebo ( $p < 0.001$ ); hazard ratio (HR) for disability progression 0.70 ( $p = 0.02$ )). However the Committee considered the clinical significance of the result for disability progression to be questionable, also noting that there was no significant effect of treatment on quality of life measures or on MRI-related measures including T1 and T2 lesion volumes and numbers of new gadolinium enhancing or T2 lesions.

---

<sup>2</sup> At its May 2012 meeting the Pharmacology and Therapeutics Advisory Committee reviewed these minutes and made the following amendment. Paragraph 9.1 change: "relapse remitting multiple sclerosis" to "relapsing remitting multiple sclerosis".

- 9.7 The Committee considered study D2201, a double blind randomised phase II study whose core component compared fingolimod 1.25 mg and 5.0 mg doses against placebo over six months (Kappos et al. *N Engl J Med* 2006;355:1124-40). The study also had an ongoing dose-blinded randomised active-treatment extension phase from month 7 onwards where two and three year interim results have been published to date (O'Connor et al. *Neurology*. 2009;72:73-9; Comi et al. *Mult Scler*. 2010;16:197-207). The Committee noted that the extension phase involved placebo-treated patients being re-randomised to either dose of fingolimod and with the fingolimod treated patients continuing at the same dose. The Committee further noted the application had presented unpublished data from the extension phase for MRI and disability changes at five years, which indicates that 60-71% of patients who had continued on fingolimod remained free of disability progression.
- 9.8 The Committee considered the TRANSFORMS trial reported by reported by Cohen et al. (*N Engl J Med* 2010; 362:402-15), which was a one year multicentre, randomised, double-blind, double dummy, parallel group phase III study. 1,281 patients with relapse remitting MS were randomly assigned (1:1:1) to 12 months treatment with once daily fingolimod 0.5 mg or 1.25 mg capsules, or interferon beta-1-alpha (Avonex) 30 ug weekly. The Committee noted that again, at baseline participants were slightly less disabled than patients meeting the NZ criteria. 53% of patients had received previous therapy with interferon-beta or glatiramer and 43% patients were treatment naïve. The Committee considered that fingolimod 0.5 mg significantly reduced relapses (ARR 0.16) compared with interferon beta-1-alpha (ARR 0.33,  $p < 0.001$ ). The Committee noted that fingolimod appeared to reduce hospitalisation and steroid use and that patient's appeared to have less severe relapses. The Committee further noted that the study was not powered to demonstrate a difference in the time to disability progression but considered that the results favoured fingolimod with the 1.25 mg dose showing a greater but not statistically significant effect on progression.
- 9.9 The Committee considered the 12 month extension study of TRANSFORMS (Khatri et al. *Lancet* 2011; 10: 520-29) involving 1,027 patients from the original study. Patients assigned to receive fingolimod in the core study continued with the same treatment and patients receiving interferon beta-1-alpha were randomly reassigned (1:1) to receive either 0.5 mg of 1.25 mg fingolimod. The Committee considered that patients receiving continuous fingolimod showed sustained benefits in ARR over the extension phase and patients who switched from interferon beta-1-alpha to fingolimod showed improvements in ARR between phases. The Committee considered that MRI parameters were significantly improved when patients were receiving fingolimod<sup>3</sup> compared with interferon beta-1-alpha during the extension study.
- 9.10 The Committee noted that in a subgroup analysis of 726 patients who had previous treatment with DMTs, the ARR was 0.26 compared with 0.53 for interferon beta-1-alpha, whilst patients who had not received prior DMTs had an average ARR of 0.15 in the fingolimod group compared with 0.31 for patients receiving interferon beta-1-alpha. The Committee noted that there were similar benefits on relapses between fingolimod and beta interferon with different EDSS states.
- 9.11 The Committee considered that there were similar rates of adverse events for patients treated with fingolimod compared with placebo, that most adverse events were mild to moderate, and that serious adverse events were more likely to be associated with the 1.25 mg dose of fingolimod. The Committee considered that when compared with beta

---

<sup>3</sup> At its May 2012 meeting the Pharmacology and Therapeutics Advisory Committee reviewed these minutes and made the following amendment. Paragraph 9.9 change: "MRI parameters were significantly improved when patients were receiving fingolimod" to "MRI parameters deteriorated significantly less when patients were receiving fingolimod".

interferon, there were similar rates of adverse events with fingolimod, however the adverse events were different. The Committee noted that the most common serious adverse events associated with fingolimod treatment were bradycardia during initiation of treatment, macular oedema, infections and skin cancers. The Committee noted that safety monitoring is recommended, including periodic ophthalmological and dermatological examinations and cardiac observation on initiation of treatment.

- 9.12 The Committee noted that the supplier seeks funding for the treatment of relapsing MS with the same Special Authority criteria as the currently funded treatments and therefore it would potentially have a role as a first line treatment. The Committee considered that fingolimod is recommended internationally for second-line use. The Committee considered that further analysis could be performed by PHARMAC staff following consideration of treatment algorithms by MSTAC and the Neurology Subcommittee. Such analysis could consider cost-effectiveness of fingolimod in those scenarios. The Committee considered that when modelling the cost utility analyses for disease progression and treatment efficacy, the assumptions for fingolimod should be consistent with the other models used for MS treatments.
- 9.13 The Committee noted the supplier's cost utility analysis which, when compared with beta interferon as first line treatment, calculated the cost per QALY of fingolimod was \$125,000 (8 QALYs per \$1 million (\$1M) net expenditure to the health sector). The Committee noted that the estimate was similar to PHARMAC estimates. The Committee considered that the PHARMAC estimate of \$180,000 per QALY (5 QALYs/\$1M), which was based on a comparison with placebo, was appropriate, particularly if fingolimod were to be funded as a last line treatment. The Committee considered the Roskell meta-analysis of disease progression, used in the supplier's analysis, had important limitations and was unclear in some of its assumptions.
- 9.14 The Committee considered that the oral dosage form for fingolimod to be an advantage, and that the disutility of injections should be factored into the analyses, particularly for glatiramer which often causes injection site reactions.
- 9.15 The Committee noted that the pivotal trials for fingolimod used 0.5 mg or 1.25 mg once daily doses. The Committee also noted that while the application for funding is for the 0.5 mg dose, studies continue to be done with the higher 1.25 mg dose despite the safety concerns with this. The Committee considered that there could be some risk that in the future, if demonstrated to be superior, that the 1.25 mg dose would be introduced with attempts to have it funded and this would likely be at higher cost.

## 10 Lead Poisoning

### Application

- 10.1 The Committee considered a funding proposal generated by PHARMAC staff to list 2,3 dimercaptosuccinic acid (DMSA) in Section B of the Pharmaceutical Schedule for the treatment of lead poisoning.

### Recommendation

- 10.2 The Committee **recommended** that DMSA be listed in the Pharmaceutical Schedule for the treatment of lead poisoning with a high priority subject to the following Special Authority criteria:

Initial application from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:

Both:

- 1 Patient has diagnosed lead toxicity and chelation treatment is recommended by Toxinz protocol ; and
- 2 The applicant has notified the Medical Officer of Health of the case if appropriate

Renewal application from any practitioner. Approvals valid for 3 months for applications meeting the criteria above and who require an additional course of treatment due to re-exposure or the need to continue treatment.

- 10.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## Discussion

- 10.4 The Committee considered the PHARMAC generated proposal to fund DMSA for the treatment of lead toxicity. The Committee reviewed the Toxinz guidelines and the safety and efficacy of currently funded treatments. The Committee noted that in New Zealand, lead toxicity above 0.72 umol/L is notifiable to the Medical Officer of Health, but chelation therapy is usually reserved for much higher levels – for children above 2.17 umol/L or in adults above 3.4 umol/L.
- 10.5 The Committee noted the pharmacodynamics of lead in the body. The Committee noted that when absorbed lead accumulates in the skeleton, muscle, brain and nervous tissue and while the lead half life in blood and soft tissues is around a month, the total body lead burden tends to increase with lifetime exposure as the skeleton acts as a sink. The Committee noted that chelation therapy can mobilise lead from where it was safely contained in the skeleton, where it cannot harm nervous tissue, back into the blood stream where it can be redistributed to CNS tissue and that this creates complex issues for treatment.
- 10.6 The Committee noted that chelation therapy is generally indicated for severe acute toxic effects, mild to moderate symptoms with moderate to high blood levels and for asymptomatic children whose blood levels are substantially elevated. The Committee considered however that a particular treatment issue that is relevant here is that when chelation with calcium disodium EDTA is carried out, some other agent must be used in conjunction in order to prevent redistribution to the brain.
- 10.7 The Committee noted that only a few people each year are treated on referral to DHB hospitals for lead toxicity - usually with calcium disodium EDTA which is given intravenously. The Committee considered that aside from their need to be located in hospital to have access to parenteral therapy many are otherwise well enough for discharge on oral chelation therapy medication with either oral agent penicillamine or DMSA.
- 10.8 The Committee considered a recent cohort study in which 500 Christchurch children were tested for iron and lead status. The Committee noted that 11 out of 450 participants had

lead above notifiable levels and a further 18 children had elevated levels above normal range. The Committee noted that this may indicate a much higher prevalence of lead poisoning than the patient population who are currently receiving treatment.

- 10.9 The Committee noted that DMSA is an analogue of dimercaprol but is water soluble and can be administered orally. Initial treatment is for five days followed by a reduced dose for 14 days. The Committee noted that a minimum of two weeks between courses is recommended to better assess rebound effects.
- 10.10 The Committee noted that for patients who are well enough to be treated in the community, DMSA would be the preferred treatment option compared with other oral chelation therapies such as pencillamine and is likely to be better tolerated.
- 10.11 The Committee considered that listing DMSA may increase the amount of screening performed for lead and that this should be considered in the budget impact analysis.
- 10.12 The Committee considered that the use of other agents may decrease and that usage of the hospital treatment calcium sodium EDTA may decrease as patients would favour an oral treatment available in the community. The Committee considered that the use of an oral treatment would also reduce costs and increase convenience for patients and reduce in-patient costs for DHBs.
- 10.13 The Committee noted that in overseas studies, the incidence of lead poisoning correlates with low socioeconomic populations, therefore there may be a higher need for similar populations in New Zealand.
- 10.14 The Committee noted that there may be some risk of DMSA being prescribed by practitioners advocating chelation therapy and therefore treatment should be targeted to patients with diagnosed lead poisoning.

## 11 Genetic and platelet function testing in targeting antiplatelet therapy

### Application

- 11.1 The Committee reviewed a memorandum from PHARMAC staff with information from a clinician on genetic and platelet function testing in targeting antiplatelet therapy.

### Recommendation

- 11.2 The Committee **recommended** that there is currently insufficient evidence for the use of genetic and platelet function testing in targeting antiplatelet therapy, either routinely or in high risk patients.
- 11.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand and (iv) The clinical benefits and risks of pharmaceuticals.*

### Discussion

- 11.4 The Committee considered that the evidence for differential platelet response to clopidogrel due to genetic variability is strong with the quality of evidence being moderate to high. The Committee noted that data so far indicate that CYP2C19 variants are associated with

variable platelet response with \*17 allele having a gain of function effect and \*2, \*3 and \*7 having reduced function effects. The Committee noted that out of these alleles, the \*2 allele appears to be the most important allele due to its prevalence. The Committee considered that the ABCB1 variant appears to be associated with a reduced function effect and this was also observed for the PON1 variant in a single study.

- 11.5 The Committee considered that in addition to genetic variables there is reasonable evidence that diabetes, obesity, gender, age, renal impairment, myocardial infarction, stenting, smoking, exercise and stress could be associated with variable platelet responsiveness to clopidogrel. The Committee noted that in addition to patient non-adherence, under dosing, poor absorption and drug interactions could also result in variable platelet inhibition.
- 11.6 The Committee considered the evidence for platelet function testing in optimising antiplatelet therapy. The Committee considered that although there is some evidence for this, the differing methods, cut-offs and lack of reproducibility limits its utility in optimising patient outcomes. The Committee noted that the GRAVITAS trial (Price et al. JAMA 2011; 305: 1097-1105) showed no benefit of a higher dose of clopidogrel (150mg/day) in patients with high on-treatment platelet reactivity. The Committee considered that further studies are required to determine the best platelet function test, the appropriate cut-off level for platelet reactivity and what high reactivity means for outcomes in individual patients.
- 11.7 The Committee considered that the strength of evidence for the use of genetic testing in optimising antiplatelet therapy was weak although the quality of evidence was good. These studies were mainly done as part of a main clinical trial with genetic sub studies done as pre-specified subgroups (Wallentin et al. Lancet. 2010; 376(9749): 1320). The Committee considered that there needs to be randomised controlled trials (RCTs) investigating the benefits of assigning treatment based on genetic and/or platelet function testing. The Committee noted that the TRIGGER-PCI trial which aimed to compare the efficacy of prasugrel versus clopidogrel in patients with high residual platelet reactivity after clopidogrel treatment was terminated due to the low rate of primary endpoint events in the study. The Committee also noted that another trial, TARGET-PCI which aims to compare guided therapy (based on platelet function or genetic testing) versus standard non-guided therapy has been suspended. The Committee noted that the GeCCO trial which is designed to assess whether clopidogrel given to patients who are CYP2C19 extensive metabolisers is non-inferior to prasugrel is currently ongoing.
- 11.8 The Committee considered that studies so far, including meta-analyses report a variable magnitude of association between CYP2C19 variant status and the occurrence of stent thrombosis for patients on clopidogrel. The positive predictive value of genetic testing for the CYP2C19 variant is low at 12% (Shuldiner et al. JAMA 2009; 302 (8): 849) which would result in a significant amount of patients being over-treated. The Committee noted that genetic testing was much more accessible now with prices ranging from \$3 to \$150 per test. The Committee considered that it is difficult to determine what genetic test has the best predictive value but noted that the positive predictive value for CYP2C19 is 12% at best based on the evidence reviewed.
- 11.9 The Committee considered that there is currently insufficient evidence to support the routine use of platelet function and/or genetic testing in clinical practice to guide antiplatelet therapy and this conclusion is consistent with international guidelines. The Committee considered that these tests need to be investigated with outcome-based randomised controlled trials (RCTs) before they can be incorporated into treatment algorithms. The

Committee considered that this assessment applies to both heterozygotes and homozygotes for the CYP2C19\*2 allele.

- 11.10 In terms of testing certain high risk patient groups, the Committee considered that there is limited value in testing patients after they have had a stent thrombosis as it would be too late after the patient has had an event. The Committee considered that there are various reasons other than genetic predisposition which could result in clopidogrel non-responsiveness as highlighted above. The Committee considered that a pragmatic approach could be to treat high risk patients (for example those with diabetes, obesity, STEMI, complex lesions) with alternative agents like prasugrel or ticagrelor without testing, if these medicines were cost-effective for the targeted group.
- 11.11 The Committee considered that there is an unmet clinical need as a significant proportion of patients on clopidogrel are not obtaining adequate platelet inhibition, exposing themselves to a risk of adverse outcomes. There is evidence that the efficacy of other therapies like prasugrel and ticagrelor is not affected by the CYP2C19 genetic variations but platelet function or genetic testing is not specific enough to target these patients.
- 11.12 The Committee noted the clinical evidence which potentially indicate that there is a greater degree of clopidogrel non-responsiveness in patients of Asian or Maori background (Luo et al. Clin Pharmacol Ther. 2006; 80:33, Man et al. J Clin Pharmacol 2010; 50: 929 and Lea et al. NZMJ 2008; 121: 33). The Committee however considered that there is insufficient evidence that there is a greater prevalence of the CYP2C19 variants in the Maori population. The Committee noted that the authors of the Lea et al paper state that “due to the fact that the Māori sample studied here was selected to possess as little non-Māori ancestry as possible, our allele frequencies should not be interpreted to be estimates of the general Māori population”.

## 12 Eculizumab for paroxysmal nocturnal haemoglobinuria

### Application

- 12.1 The Committee reviewed an application from Alexion Pharmaceuticals for the listing of eculizumab (Soliris) on the Pharmaceutical Schedule for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

### Recommendation

- 12.2 The Committee **recommended** that the application for eculizumab (Soliris) in paroxysmal nocturnal haemoglobinuria (PNH) be declined. The Committee also recommended that the application for eculizumab in PNH be referred to the Haematology Subcommittee for consideration.
- 12.3 The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services and* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 12.4 The Committee noted that the evidence for eculizumab was mainly from observational studies with only one randomised controlled trial, the TRIUMPH study which was not powered to detect differences in either thrombosis rates or mortality. The TRIUMPH study (Hillmen et al. *N Engl J Med.* 2006; 355: 1233) was a double-blind, multi-centre, placebo-controlled trial involving 87 patients over a period of 6 months. The primary outcome of the trial was stabilisation of haemoglobin levels and transfusion requirements with a number of secondary outcome variables including the FACIT-Fatigue QOL score. The Committee considered that the findings from the study supports the claim that eculizumab does alleviate the haemolysis associated with PNH and the associated sequelae, thus improving symptoms and the quality of life for these patients. The Committee however noted that the study was not able to address the impact on life-threatening complications as only one thrombosis (in the placebo arm) occurred over the six month study period and there were no deaths.
- 12.5 The Committee considered that one of the major issues with eculizumab is its cost. The Committee considered that because the treatment with eculizumab does not alter the underlying defect of the disease, with the need for continued life-long therapy (unless spontaneous remission occurs in a minority of patients), it is crucial to understand the impact of eculizumab on mortality.
- 12.6 The Committee noted that the natural history studies on PNH have provided differing views on survival. The Committee noted that in Table 4 of the main submission, the supplier quotes a median survival ranging from 10 to 25 years. The Committee also noted a French cohort study (de Latour et al. *Blood* 2008; 112: 3099) of 460 PNH patients which showed a median survival of 22 years in the pre-eculizumab era with a 76.3% 10-year survival rate and more importantly a 92% 10-year survival rate in the 83 patients diagnosed after 1996. The Committee noted that this paper was not presented in Table 4 where survival rates were presented.
- 12.7 The Committee noted that the supplier put a significant amount of emphasis on the study by Kelly et al (*Blood* 2011; 117: 6786) from Leeds which attempted to address the issue of the natural history of PNH with a single centre review of 79 consecutive patients on eculizumab with a cohort of 30 patients treated in the 7 years before the availability of eculizumab. The Committee noted that there were 3 deaths in the eculizumab arm compared to 5 deaths in the historical group. The Committee noted that the Kaplan-Meier survival curves showed a statistically significant difference ( $p=0.01$ ) in the 5-year survival in the eculizumab arm versus the historical cohort, 95.5% (95% CI 87.6% - 98.5%) versus 66.8% (95%CI 41.4% - 85.1%). The Committee however considered that there was nearly an overlap in the two confidence intervals. The Committee also considered that it was unclear from the study why the period of 7 years was chosen. The Committee considered also that the comparison is lacking in many details with no description on the causes of death of the five individuals or even if the cohorts are matched in terms of age, sex or other co-morbidities. The Committee noted that an attempt to obtain more information from the primary author did not provide more confidence in the quality of the evidence.
- 12.8 The Committee noted the results from another publication from the same Leeds group, Hall et al (*Blood* 2003; 102: 3587) which looked at the natural history of PNH in the time preceding the availability of eculizumab. The Committee noted that the primary outcome of the paper was to investigate the role of warfarin as primary prophylaxis in preventing thrombosis in PNH but it also contained information on mortality. The Committee noted that the paper reviewed data on 163 of 179 consecutive patients with PNH clones investigated in the Leeds Laboratory prior to 2002. The Committee noted that of the 163 patients studied, with a median follow-up period of 6 years (range 0.2-38 years), there

were 20 deaths (12.5%) of which 8 were attributable to PNH (4 attributed to liver thrombosis), 6 to aplasia and 5 probably unrelated to PNH with 1 unknown case. The Committee noted that the 5-year survival in this cohort is therefore greater than 87% which raises the suspicion that the Leeds group could have chosen the 7-year period for the Kelly et al (Blood 2011; 117: 6786) historical comparison to obtain a statistically significant result of reduced mortality with eculizumab. The Committee considered that if there was no survival advantage with eculizumab and only a reduction in blood transfusion requirements and fatigue, the cost per QALY for eculizumab would be very large. The Committee considered that the supplier estimation of an incremental gain of 32.5 life years for patients who receive eculizumab is too high.

- 12.9 The Committee noted that Hillmen et al (Blood 2007; 110: 4123) implies that the rate of thromboembolism is markedly reduced from 7.37 events/100 patient years prior to the usage of eculizumab to 1.07 events/100 patient years after commencing treatment. The Committee also noted that the authors concluded that “Considering that thrombosis has been demonstrated to cause the majority of deaths in PNH, it is reasonable to expect that eculizumab treatment, by decreasing the risk of thrombosis, may increase the life expectancy of these patients”. The Committee considered that although the data from the Hillmen et al study is quite compelling, the reduction in the rates of thromboembolism from before to after treatment may have an alternative explanation. The Committee considered that because thrombosis may lead to the diagnosis of the condition in the first place, it could be that thrombosis occurs earlier in the time course of the disease.
- 12.10 The Committee considered that there would be an increased risk of infections with eculizumab use – particularly meningococcal disease with 19 cases and 4 deaths resulting in a rate of 0.46/100 patient years of exposure (supplier submission). The Committee noted that because the serotype B meningococcal strain remains a significant New Zealand strain and cannot be prevented long term with currently available vaccines, not all meningococcal disease would be prevented with vaccination.
- 12.11 The Committee noted that the supplier’s estimates of PNH prevalence in New Zealand is possibly an overestimate but it is likely that uptake of eculizumab would be higher than the 35-50% range indicated by the supplier. The Committee considered that there was an unmet clinical need for PNH treatments. The patients most likely to benefit from treatment with eculizumab are those in need of frequent transfusions and those with a history of thrombosis. However, the Committee considered that given the uncertainty regarding mortality benefit, the effect of treatment with eculizumab is not in proportion to its current cost.

## 13 Eltrombopag for idiopathic thrombocytopenic purpura

### Application

- 13.1 The Committee reviewed an application from GlaxoSmithKline for the listing of eltrombopag (Revolade) on the Pharmaceutical Schedule for the treatment of idiopathic thrombocytopenic purpura (ITP).

### Recommendation

- 13.2 The Committee **recommended** that the application for eltrombopag (Revolade) for the treatment of idiopathic thrombocytopenic purpura (ITP) be referred to the Haematology Subcommittee for consideration; including for further advice on the recommended Special

Authority criteria. The Committee also **recommended** that PHARMAC staff conduct a cost-utility analysis for review by PTAC.

- 13.3 The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (ii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iii) *The clinical benefits and risks of pharmaceuticals;* and (iv) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services..*

## Discussion

- 13.4 The Committee noted that the annual incidence of ITP is approximately 2.5 per 100,000 in adults and unlike the disease in children, very few adults (approximately 10%) achieve a spontaneous remission. The Committee also noted that the lifetime risk of fatal bleeding is 5% for all patients and the risk of serious or fatal bleeds is related to age and time that the platelet count is below 30,000 per  $\mu\text{L}$ . The Committee noted that the rates of serious or fatal bleeding vary greatly between newly diagnosed patients and those with chronic, refractory ITP who tend to do very poorly. Using a Markov model, the Committee noted that the risk of fatal bleeding is 0.4% per year for a 40-year old and 13% per year for a 60-year old with platelets  $< 30,000$  per  $\mu\text{L}$  persistently.
- 13.5 The Committee noted that the focus of current available therapies is to reduce platelet destruction. The Committee considered that first line therapy for ITP is steroids or Anti-D immunoglobulin and intravenous immunoglobulin (IVIg) is given in the event of bleeding. The Committee considered that a splenectomy can be done if the patient's platelet count does not improve after the above therapies but up to 34% are refractory to this or only have a short-term improvement. The Committee considered that approximately 20% of patients are resistant to first and second line therapies as well as splenectomy with another 15% relapsing post-splenectomy (Garnock-Jones. *Drugs* 2011; 71 (10): 1333).
- 13.6 The Committee noted that eltrombopag is an orally active thrombopoietin receptor agonist. They also noted that because eltrombopag inhibits the UGT, CYP2C8 and CYP2C9 enzymes as well as the BCRP (breast cancer resistance protein) and OATP1B1 transporters, it is likely to interact with statins.
- 13.7 The Committee noted that the strength of evidence for eltrombopag was moderate but of good quality. The Committee noted that the results of the Bussel et al trial (*Lancet* 2009; 373: 641) which showed that for the primary endpoint of patients achieving platelet counts of 50 000 per  $\mu\text{L}$  or more at day 43, eltrombopag resulted in significant benefit when compared to standard of care (59% versus 16%, OR 9.61, 95% CI 3.31-27.86,  $p < 0.0001$ ). The Committee noted that about 50% of patients ended up on the higher dose of 75mg and a third of patients did not respond to either dose. The Committee noted that of patients who started with a lower platelet count of  $< 15,000$  per  $\mu\text{L}$ , 50% managed to obtain platelet counts of 30,000 per  $\mu\text{L}$  and this rate was not significantly different from patients with higher baseline platelet levels. The Committee noted that response rates to eltrombopag did not differ based on splenectomy status, patient age or previous treatment. The Committee noted that the response to eltrombopag was sustained for the 6 week period of the trial but returned to baseline 2 weeks after stopping treatment.
- 13.8 The Committee considered that the bleeding rates were reported ambiguously in the trial with no clinically significant bleeding (WHO grade 2-4) in patients with platelet counts  $> 50,000$  per  $\mu\text{L}$ . However, in the placebo arm there was one cerebral haemorrhage and one gastrointestinal. In the eltrombopag arm, there was also one gastrointestinal

haemorrhage and cerebral haemorrhage, but these were both in non-responders (both of whom had platelets <50,000 per  $\mu\text{L}$ ).

- 13.9 The Committee also noted that 60% of patients in the placebo group versus 39% in the eltrombopag group reported bleeding during the trial (OR 0.27, 95% CI 0.09-0.88,  $p=0.029$ ). The Committee noted that more patients (6 versus 1), in the eltrombopag arm had increased transaminases two times the upper limit of normal.
- 13.10 The Committee noted the results of the RAISE trial (Cheng et al. Lancet 2011; 377: 393) which was a 6-month Phase III, double-blind, randomised controlled trial (RCT) which aimed to look at the safety and tolerability of eltrombopag. The Committee noted that 17 of the 197 patients randomised stopped early, 13 in the eltrombopag arm and 4 in the placebo arm (out of which 1 was due to a fatal brain stem haemorrhage). The Committee noted that from day 15 until the end of treatment, the median platelet count was 53,000-73,000 per  $\mu\text{L}$  in the eltrombopag arm and 17,000-23,000 per  $\mu\text{L}$  in the placebo arm despite use of rescue therapies in 40% of patients on placebo treatment. The Committee noted that the odds of clinically significant bleeding (WHO grade 2-4) were 33% for the eltrombopag arm versus 53% for the placebo. The Committee also noted that 59% of patients on eltrombopag versus 32% placebo had reduced or stopped baseline treatments (OR 3.1, 95% CI 1.24-7.75,  $p=0.02$ ) and rescue treatments were given to 18% of eltrombopag patients versus 40% of placebo patients (OR 0.33, 95%CI 0.16-0.64,  $p=0.001$ ). Platelet transfusions were given to 5% of the eltrombopag recipients versus 6% of placebo with 13% and 27% respectively started on a new treatment. The Committee noted that the evidence for stopping treatments in the eltrombopag group was not strong as some of the patients in the eltrombopag arm were non-responders.
- 13.11 When considering the improvement in the quality of life, the Committee noted that patients on eltrombopag had improvements in 5 out of 8 domains of the SF-36v2 score compared to no improvements in the placebo group.
- 13.12 The Committee noted that more patients in the eltrombopag arm had alanine aminotransferase (ALT) rises (9 versus 2 patients) which resolved (6 patients while still on treatment and 3 patients stopped treatment). The Committee noted that 5 patients had bilirubin rises, all in the eltrombopag arm, which is an important issue in the context of eltrombopag being an OATP1B1, BRCP and possibly a UGT1A1 inhibitor. Bilirubin requires UGT1A1 for metabolism, and if inhibited, this could lead to hyperbilirubinaemia. The Committee noted that 2 patients on eltrombopag had a venous thromboembolism (VTE) but other risk factors were present in those patients.
- 13.13 The Committee noted the results of the EXTEND trial in abstract form (Saleh et al. Blood 2008; 112: 401) which showed that 75% of the patients refractory to prior treatments achieved platelet counts >50,000 per  $\mu\text{L}$  compared to 84% of non-refractory patients ( $p=0.14$ ). The Committee noted that the refractory group had more episodes of clinically significant bleeding but this was reduced 50% from baseline.
- 13.14 The Committee considered that if funded, eltrombopag would be used in combination with current ITP treatments which unfortunately have very limited efficacy. The Committee considered that the evidence suggests that eltrombopag does improve the quality of life for patients, reduce major bleeds and death as well as reduce the cost of transfusions. There could however be an increased risk of VTEs. The Committee considered that the estimate of patient numbers by the supplier appears to be an overestimate but further advice should be sought from the Haematology Subcommittee. The Committee considered that the supplier's estimate of baseline mortality rate of 2.76% per annum was acceptable and the

rate could potentially be higher (up to 13% per annum) if eltrombopag is restricted to a higher risk group.

- 13.15 The Committee considered that eltrombopag, if funded, could be restricted with criteria stricter than the trial entry criteria. The Committee considered that it should be restricted to use by haematologists with Special Authority criteria targeting it to patients with chronic ITP with platelet counts <30,000 per  $\mu\text{L}$  (possibly restricting it further to those in this group with a history of bleeding), in whom splenectomy has been deemed inappropriate<sup>4</sup> by at least 2 surgeons and other treatments including steroids and Anti-D have proven ineffective. The Committee considered that the supplier's estimation of patients who are unable to undergo splenectomy of 70% seems very high.
- 13.16 The Committee also considered that clinical response to eltrombopag would be observed within 2 weeks of treatment initiation. The Committee considered that about a third of patients would not respond to eltrombopag and there is no evidence that they would still achieve the outcome of reduced bleeding if treatment was continued. The Committee considered that the supplier's estimation of cost offsets from the reduced use of other treatments like rituximab and IVIg in responders is acceptable.
- 13.17 The Committee sought advice from the Haematology Subcommittee in regards to this application and the proposed Special Authority criteria. The Committee also sought the advice of the Subcommittee in regards to the risk of bleeding with the following successive lower levels of platelet counts; >50,000 per  $\mu\text{L}$ , 30,000 to 50,000 per  $\mu\text{L}$ , 10,000 to 30,000 per  $\mu\text{L}$ , 5,000 to 10,000 per  $\mu\text{L}$ , <5,000 per  $\mu\text{L}$ , and functional zero or undetectable platelets and the current treatments (i.e. steroids, IVIG and platelet transfusions) which would be administered at those levels. The Committee considered that the lower limit of 30,000 platelets per  $\mu\text{L}$  could potentially be reduced further to target eltrombopag to those at greatest risk.

---

<sup>4</sup> At its May 2012 meeting the Pharmacology and Therapeutics Advisory Committee reviewed these minutes and made the following amendment. Paragraph 13.15 change: "in whom splenectomy has been deemed inappropriate" to "in whom splenectomy has been deemed inappropriate or ineffective".